Odesa National Medical University
Department of Pharmacology and Pharmacognosy

# AGENTS ACTING ON CARDIOVASCULAR SYSTEM.

# CARDIOTONICS.

# ANTIARRYTHMIC AGENTS

# CARDIAC GLYCOSIDES (CG) –

*(greek. “glikis” - sweat)*

***Substances of plant origin that consist of 2 parts: nitrous-free (aglycon) and sugary (glycon), which possesses the cardiotonic and cardiotrophic actions, used for the treatment of heart failure***

**Foxglove**
***(Digitalis)***

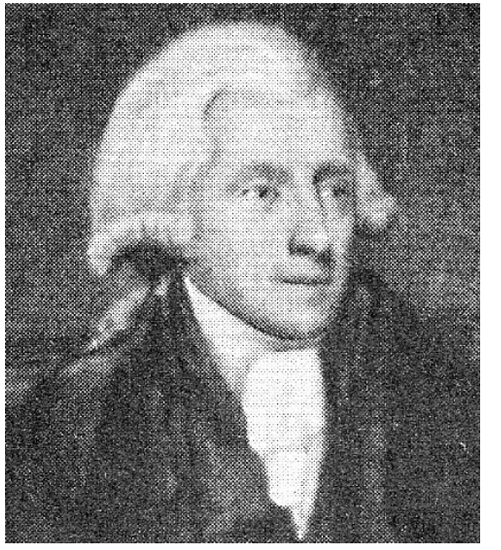
**Strophantus**
***(Strophanthus)***

**Adonis**
***(Adonis vernalis)***

**Lily of the valley**
**(*Convallaria*)**

# ИСТОРИЯ СОЗДАНИЯ СГ

**в 1785 году У. УИЗЕРИНГ**
**ввел в клиническую практику наперстянку**

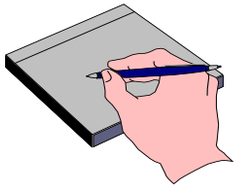


**в 1865 году Е.В. ПЕЛИКАН**
**исследовал действие строфанта на сердце лягушки**

**в 1880-х г.г. в клинике С.П. БОТКИНА и лаборатории И.П. ПАВЛОВА**
**были детально исследованы и внедрены в клинику другие лекарственные растения, содержащие сердечные гликозиды – горицвет (Н.А.Бубнов), ландыш (И.П.Богоявленский), морозник (Н.Я.Чистович)**

# CLASSIFICATION OF CARDIAC GLYCOSIDES

- **Long-acting agents with significant cumulation :**
  - **Ladyfingers *(Digitalis purpurea)* – digitoxin, cordigit**
- **Intermediate-acting agents with middle cumulative properties :**
  - **Woolly foxglove *(Digitalis lanata)* – digoxin, celanide, lantoside**
  - **Adonis spring *(Adonis vernalis)* – adoniside**
- **Short-acting agents with insignificant cumulation:**
  - **Strophantin *(Strophanthus)* – strophantin**
  - **Lily of the valley *(Convallaria majalis)* – corgylcon, tincture of convallaria**



# STRUCTURE OF CARDIAC GLYCOSIDES

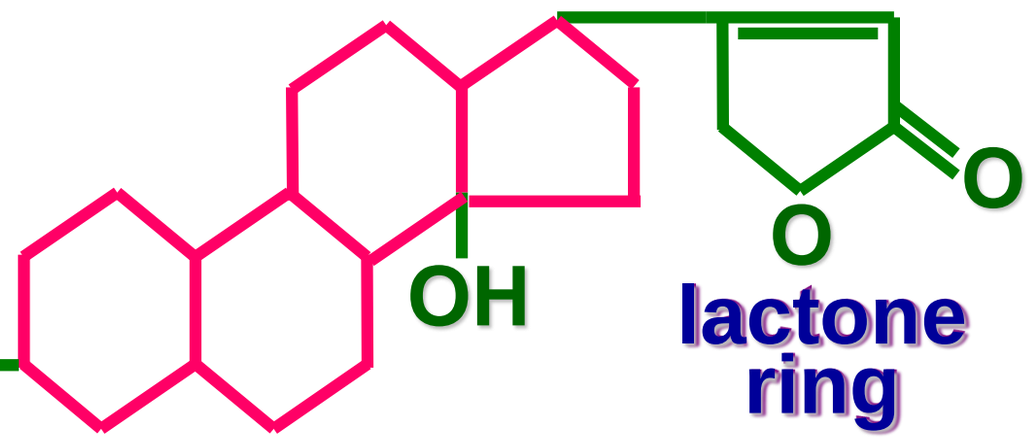
**glycon** — **O** — **aglycon**

**n=1 – monozide**
**n=2 – diozide**
**n=3 – thriozide**
**n=4 – tetrazide**

*n – number of molecules*

Activity

**steroid spirit**
*(der. Cyclopentane perhydrophenantrene*




**sugary part** — **O** —

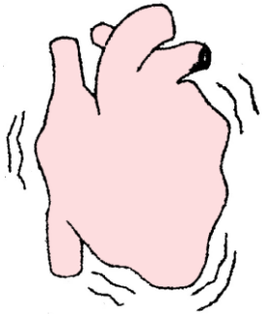
**pharmacokinetic and biological activity in general**

**cardiotonic properties**

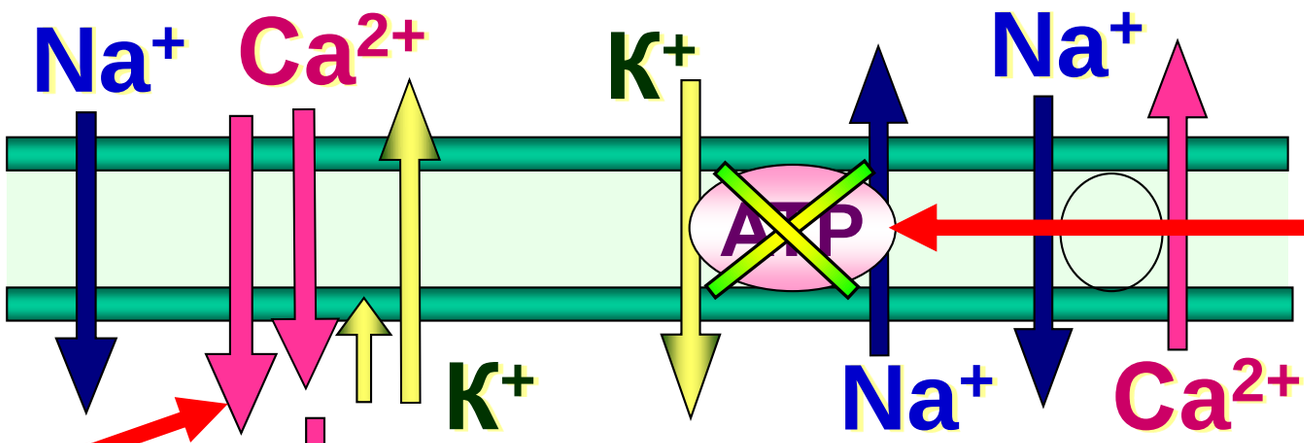
# PHARMACODYNAMIC OF CARDIAC GL.

## cardiac glycosides:

- «+» inotropic (systolic) – increasing and shortening of systole
- «+» tonotropic – ↑ myocardial tonus
- «–» chronotropic (diastolic) – ↓ heart rate
- «–» dromotropic – ↓ conductivity
- «+» bathmotropic – ↑ excitability



# MECHANISM OF THE CARDIOTONIC ACTION OF CARDIAC GLYCOSIDES

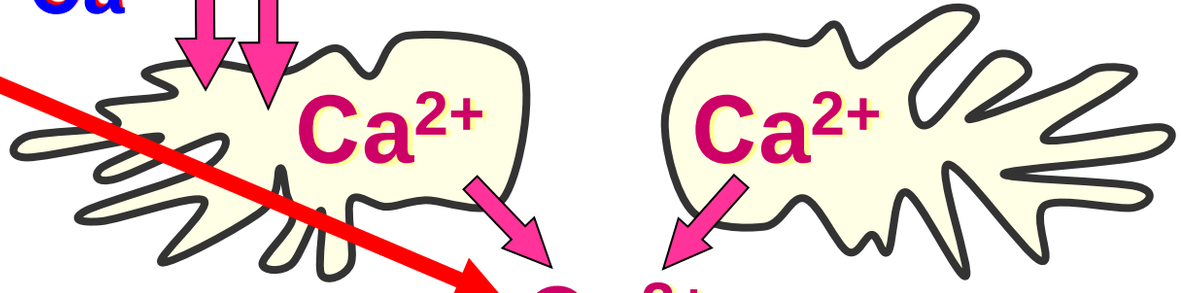



## I – membrane excitation

CG

block SH-group of ATP-ase $Na^+, K^+$-pump, ↓ $K^+$, ↑ $Na^+$, $Ca^{2+}$

CG ↑ $Ca^{2+}$




## II – coupling of excitation and contraction

ATP → myosin

actin G → actin F

CG

## III – contraction

↑ $Ca^{2+}$, conversion of globular actin (G) into fibrillar (F), ATP-activity of myosin

actinomyosin

# PHARMACODYNAMICS OF CG

## according to «+» inotropic effect:

- $Ca^{2+}$ –CG enhancer
- $K^{+}$ and SH-group donators (unithiol etc) – CG antagonists

- «+» tonotropic: ↓ size of previously dilated heart
- «–» chronotropic (diastolic):
  - ✓↑ vagus influence in reflex way from baroreceptors of sinocarotid zone and myocardium – «vagal factor»;
  - ✓↓ reflex tachycardia because of direct anti-adrenergic impact –«extra-vagal factor»
- cardiotrophic: restoring energy, lipid balance, ↓ $O_2$ consumption, liposomal stabilization, ↓ tissue hypoxia

# ECG CHANGES


***inborn valve abnormality***

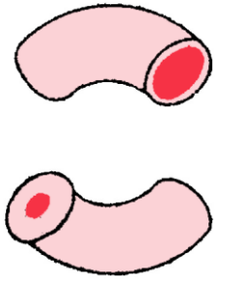
***after glycosides***

## In the therapeutic doses:

- ↓ T wave (early symptom - ↑ tissue metabolism), ↓ ST down from isoelectric line, ↓ QRST (sign of «+» inotropic effect);
- ↑ PP interval («-» chronotropic effect),
- modest ↑ PQ («-» dromotropic effect)

# PHARMACODYNAMICS OF CG

## non-cardiac effects:



- **hemodynamics:**
  - ↑ cardiac output
  - Arterial BP may ↓ or ↑ (become normal)
  - ↓ venous pressure (unloading of venous compartment of systemic circulation)
  - ↓ diastolic pressure in the ventricles
    ↑ sub-endocardiac bloodflow
  - ↓ of pressure in pulmonary circulation (improvement of gases exchange → decreasing of cyanosis, dyspnoea, tissue hypoxia, metabolic acidosis)
  - ↑ systemic and cerebral blood circulation

# PHARMACODYNAMICS OF CG

## non-cardiac effects:

- **kidneys: diuretic effect *via*:**
  - **↑ renal blood flow and glomerular filtration**
  - **↓ reabsorption of water, $Na^+$, and $Cl^-$:**
- **blood coagulation: ↓ blood coagulation (corglycon), ↑ blood coagulation (foxgloves' agents, strophantin)**
- **CNS: sedation (medicines of Lily of valley and Adonis)**

# PHARMACOKINETICS CG

| *Indexes* | Foxgloves' group | Strophantin group |
|---|---|---|
| GIT asborption | 70-96 % (lipid-soluble), | 3-8 % (water-soluble) |
| route of administrat. and onset of action | oral (0,5-2 hrs), I.V. (5-30 min) | I.V. ! (after 2-5 min) |
| plasma protein binding | tight (20-97 %) | слабая (10-20 %) |
| T ½ | digoxin – 40 hrs<br>digitoxin – 168 hrs | 20-25 hrs |
| cumulation | significant ! | low |

# INDICATIONS FOR CARDIAC GLYCOSIDES

- **acute heart failure** (corglycon, strophantin, digoxin I.V., diluted with **sodium chloride solution!**)
- **chronic heart failure :** decompensated heart valve abnormalities, cardiosclerosis, overloading of myocardium at arterial hypertension etc. (for oral intake)
- **supraventricular tachycardia (!):** paroxysmal tachycardia, atrial flutter, and atrial fibrillation

# MANAGEMENT OF CG DOSING

## principles of digitalization:

- **saturation phase:**
  - **rapid (during 1 day - 100 % of full-dose)**
  - **intermediate (3-4 days; at 1-st day – 1/2 of full-dose)**
  - **slow (5-7 days; at 1-st day – 1/4 of full-dose)**
- **maintaining phase (long-lasting): maintaining dose = full-dose x elimination (%) / 100 %**

## Symptoms of the therapeutic level of digitalization:

- **normal heart rate instead of tachycardia**
- **transformation of tachysystolic form of atrial fibrillation into bradysystolic, elimination of pulse deficit**
- **↓ clinical symptoms of heart failure (dyspnoe, cyanosis, oedema, ↑ daily diuresis), ↓ liver size**

# INTOXICATION BY CG

- «–» dromotropic – suppression of AV-conductivity (↓ PQ, dropping-out of QRS):
- «+» bathmotropic – alteration of conductivity + automacity ⇒ ectopic areas (around 20 types of arrhythmia, especially ventricular)

**cardiac symptoms (50-90 %):**

→ initially – bradycardia with ectopic beats

→ followed by tachycardia with sharp ↑ BP

→ then ventricular tachyarrhythmia upto ventricular fibrillation and death !

# INTOXICATION BY CG

## extra-cardiac effects:

- **GIT-disturbances (75-90 %):** anorexia, vomiting spasm of intestine, diarrhea (↑ vagal tonus), intestinal necrosis (spasm of splanchical vessels) – as the rule, develop before cardiac symptoms!
- **neurological (30-90 %):** xantopsia (95 %), headache, insomnia, neuralgia of n.trigeminis and n.facialis
- **others (rare) –** bronchospasm, allergy, thrombocytopenia, gynecomastia

# TREATMENT OF GC INTOXICATION

- at the beginning – lowering of dose; at the advanced stage – agents withdrawal and usage of charcoal (50-100 gr) or cholestiramine (4-8 gr)
- K+ containing agents (panagin, "polarizing combination" – solution of KCl in 5 % glucose sol. with insulin and ascorbic acid)
- donators of SH-group (unithiol,acetylcystein)
- chelators (EDTA)
- anti-arrhythmics (lidocaine, phenytoin)
- ascorbic and panthotenic acid
- digibind (antibodies to foxgloves' medicines)

# NON-GLYCOSIDE CARDIOTONICS

## classfication

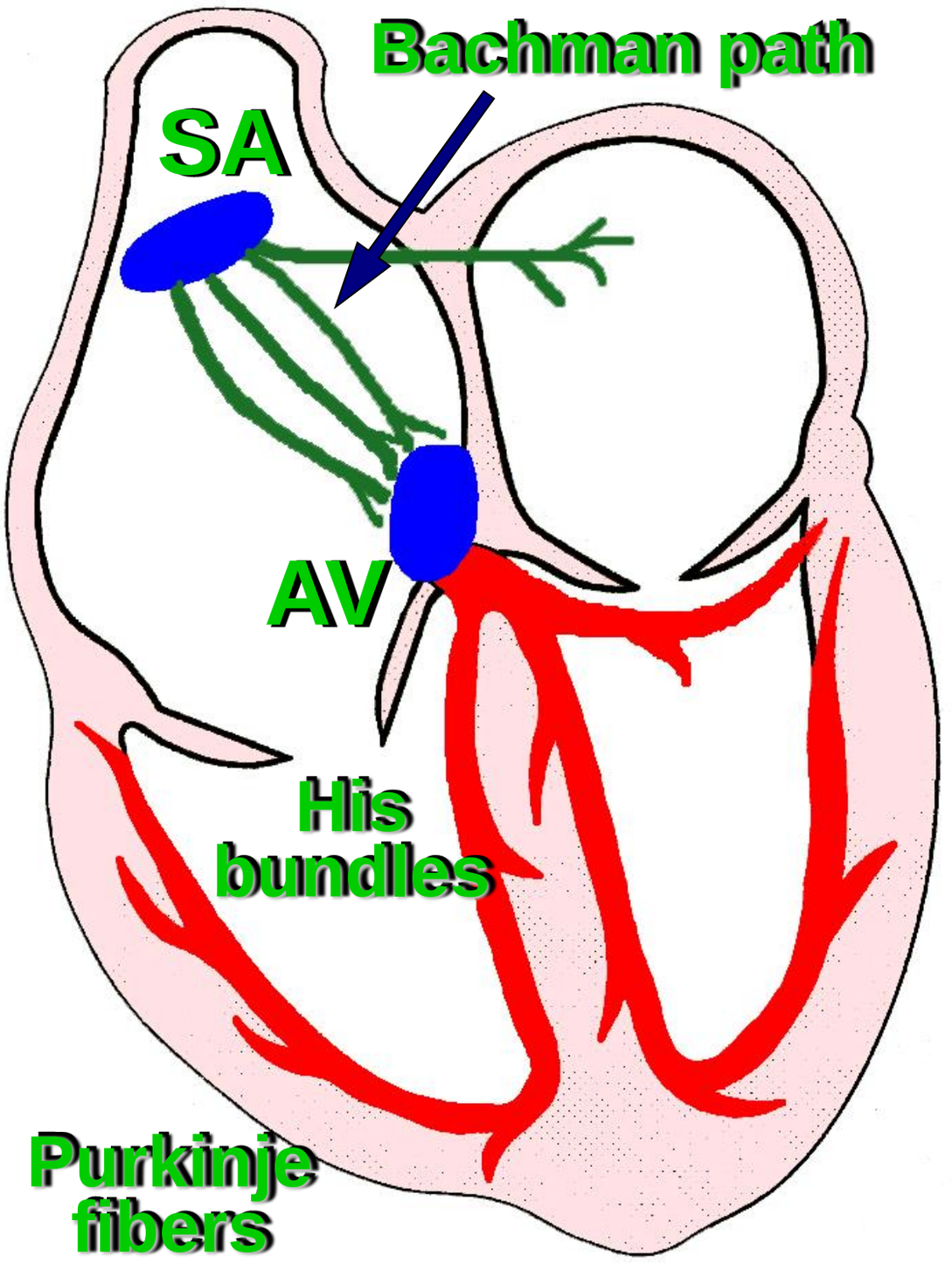
- adrenomimetics* – dopamine, dobutamine etc.
- phosphodiesterase inhibitors* – amrinone, milrinone
- calcium sensitizators* – levosimendan
- metabolic agents – glucagon, riboxin, glutamic acid etc.

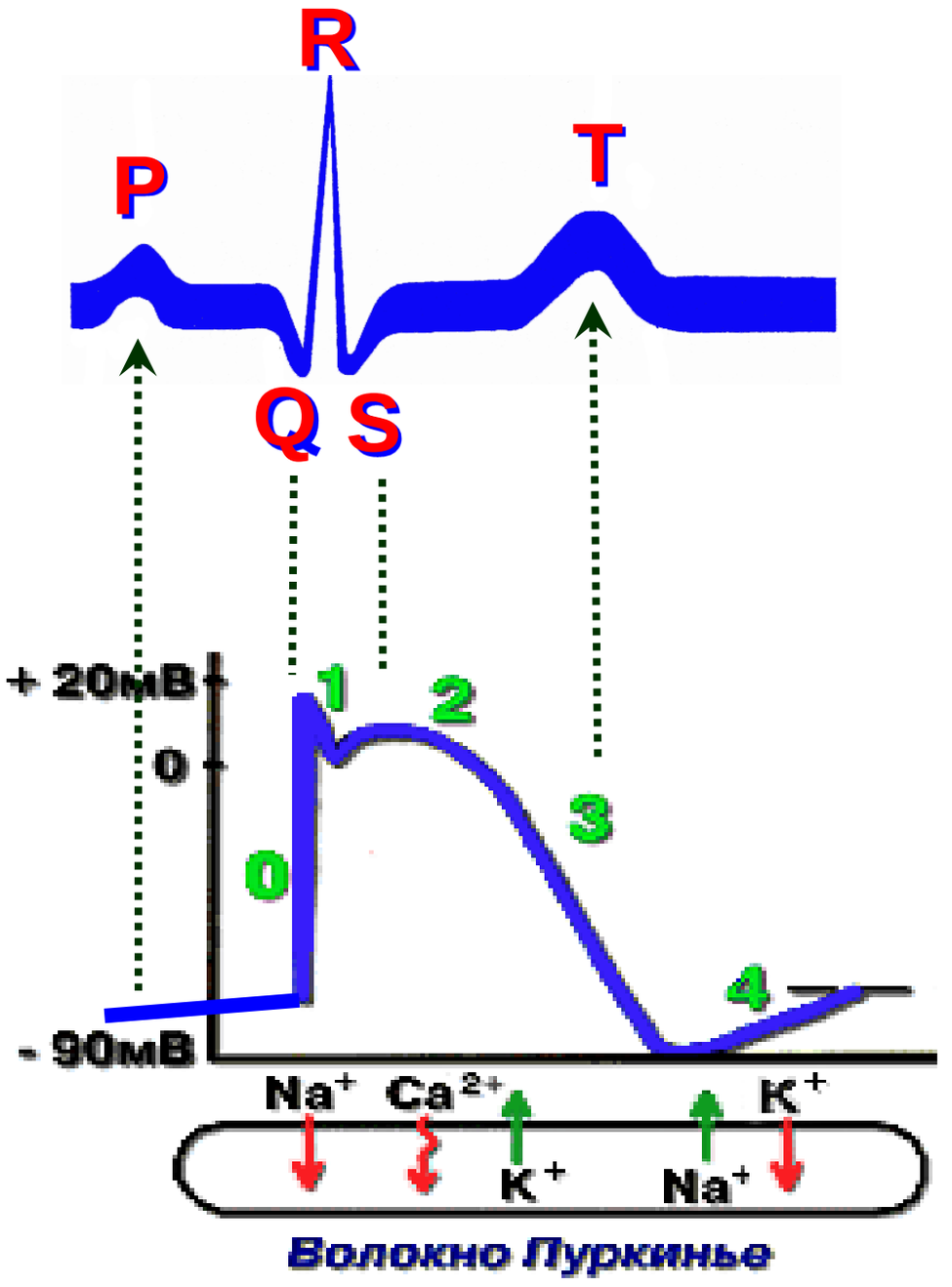
## *indications

- cardiogenic shock (dopamine, dobutamine)
- advanced heart failure of III-IV classes that resistant to glycoside therapy (dobutamine, milrinone etc.)

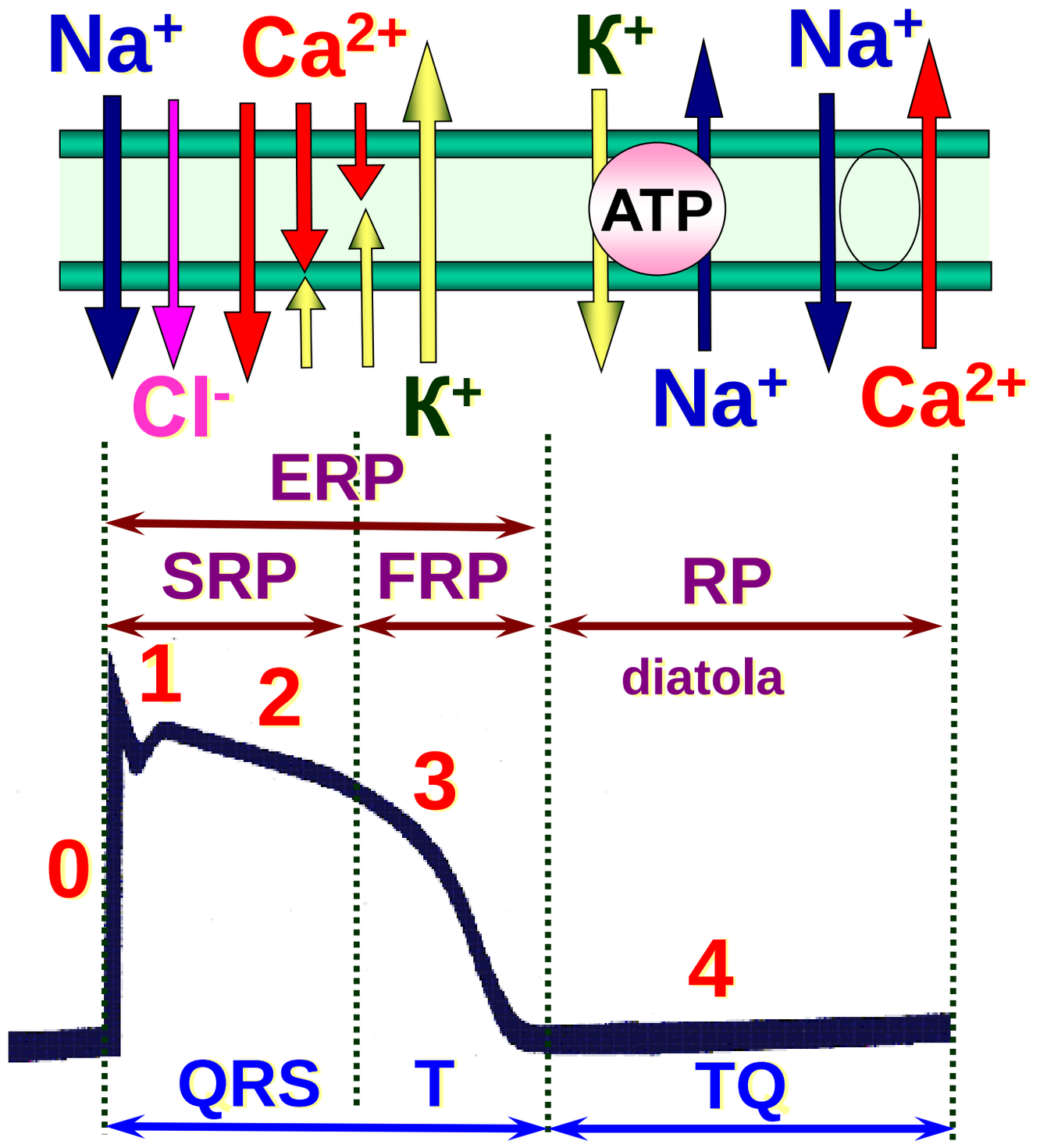
# ANTI-ARRHYTHMIC AGENTS

# CARDIAC CONDUCTIVE SYSTEM



# CARDIAC ELECTROPHYSIOLOGY




## Phases of action potential (AP):

**0 – rapid depolarization** (rapid influx of $Na^+$)

**1 – starting rapid repolarisation** (influx of $Cl^-$)

**2 – plateau** (influx of $Ca^{2+}$)

**3 – final rapid repolarisation** (outflux of $K^+$)

**4 – diastolic depolarization** ($Na^+$, $K^+$-pump)

# ARRHYTHMIAS –

***abnormal processes of depolarisation in myocardium:***

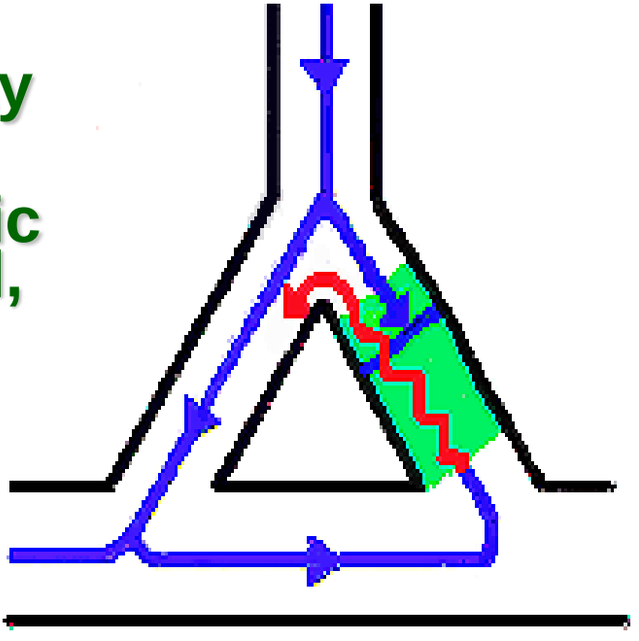
- ✓ ***according to loci of impulse appearance (any non-sinus rhythm)***
- ✓ ***their frequency (< or > 60-90 per min)***
- ✓ ***regularity (incorrect)***
- ✓ ***way of transmission***

## types:

- **tachyarrhythmia**
- **bradyarrhythmia**
- **supra-ventricular**
- **ventricular**

## pathogenesis:

- **upset of impulse generation – automaticity of SA-node, pathologic automaticity (ectopic areas), early and late depolarisation**
- **upset of conductivity – simple physiologic refractiveness, it's prolongation, ↓ rest potential, fading impulse transmission, n re-entry phenomenon, disturbance of trans-cellular electrotonic interaction etc**



# ARRHYTHMIA

## principles of pharmacotherapy:

- **ethiotropic** – correction of:
  - neurogenic and endocrinic disturbances (угнетающие ЦНС, антитиреоидные)
  - inflammation of myocardium (NSAIDs, glucocorticoids)
  - acute and chronic ischemia of myocardium (angioprotectors, coronarodilators etc.)
- **pathogenetic** – removing of disturbances of:
  - electrolyte balance in different phases of cardiac cycle and associated abnormalities of automaticity and excitability (membrane-stabilizing, $Ca^{2+}$ and $K^{+}$ channels blockers, potassium-containing agents)
  - neural regulation of cardiac functioning (conductivity) – for tachyarrhythmias (beta-adrenergic blockers), for bradyarrhythmias (M-cholinergic blockers, beta-adrenomimetics)

# SITES OF ACTION OF ANTI-ARRHYTHMIC AGENTS

## I. Influence of heart:

I. refractive period (↑ non-susceptibility)

- automacity (↓ diastole, depolarisation, ↑ excitability threshold)
- conductivity (↑ P-R, ↑ R-R)
- excitability (↓)
- contractility (↓)

## II. Influence on efferent innervation:

- in tachyarrhythmia disturbances (↓ sympathetic and ↑ cholinergic innervations)
- in bradyarrhythmia disturbances (↓ cholinergic and ↑ sympathetic innervations)

# DEMANDS FOR THE IDEAL ANTI-ARHYTHMICT AGENT

- effectiveness at different types of arrhythmia
- absence of negative impact on cardiac contractility and coronary blood flow (especially at myocardial infarction and heart failure)
- broad wideness of therapeutic action (!)
- possibility of long-lasting usage (for years)
- long-lasting anti-arrhythmic effect (at least 12-24 hrs)

# CLASSIFICATION OF ANTI-ARRHYTHMICS

**for tachyarrhythmias:**

⇒ **I class – sodium channels blockers (membrane-stabilizing agnets):**

- **I A –** ***those that prolong effective refractive period (ERP):*** **quinidine, novocainamide, disopyramide etc.**
- **I B –** ***those that shorten ERP:*** **lidocaine, diphenin etc.**
- **I C –** ***those with different influence on ERP:*** **propafenon, etacizin etc.**

⇒ **II class – β-adrenoblockers: propranolol, atenolol, metoprolol etc.**

⇒ **III class – potassium channels blockers: amiodarone, sotalol, ibutilide etc.**

⇒ **IV class – calcium channels blockers: verapamil, halopamil, diltiazem**

⇒ **V class – those that normalize electrolytes equilibrium: panangin, potassium chloride etc.**

# SODIUM CHANNELS BLOCKERS

## (membrane-stabilizing)

**I A** – quinidine, novocainamide, disopyramide etc.

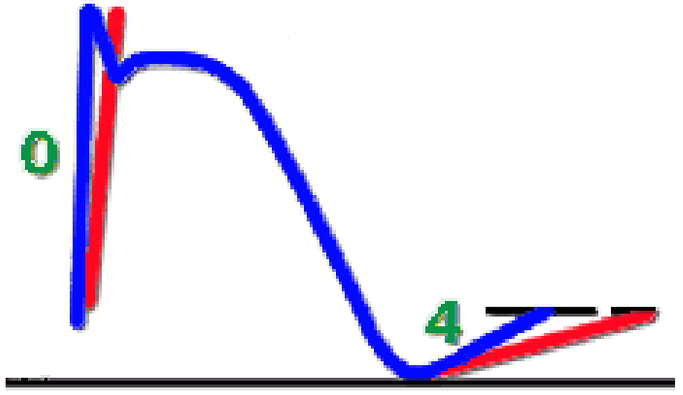
**I B** – lidocaine, diphenin etc.

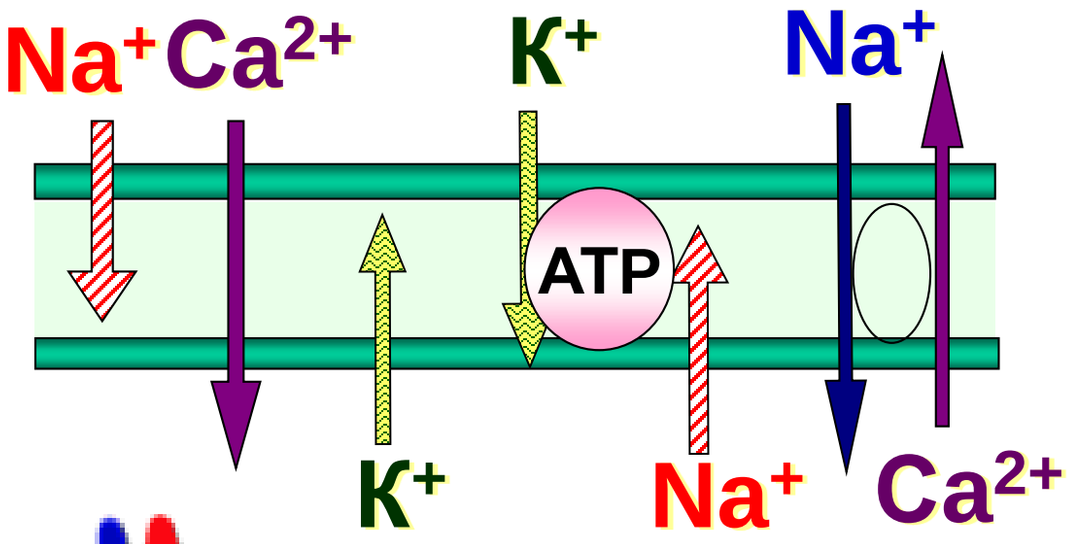
**I C** – propafenone, etazicin etc.

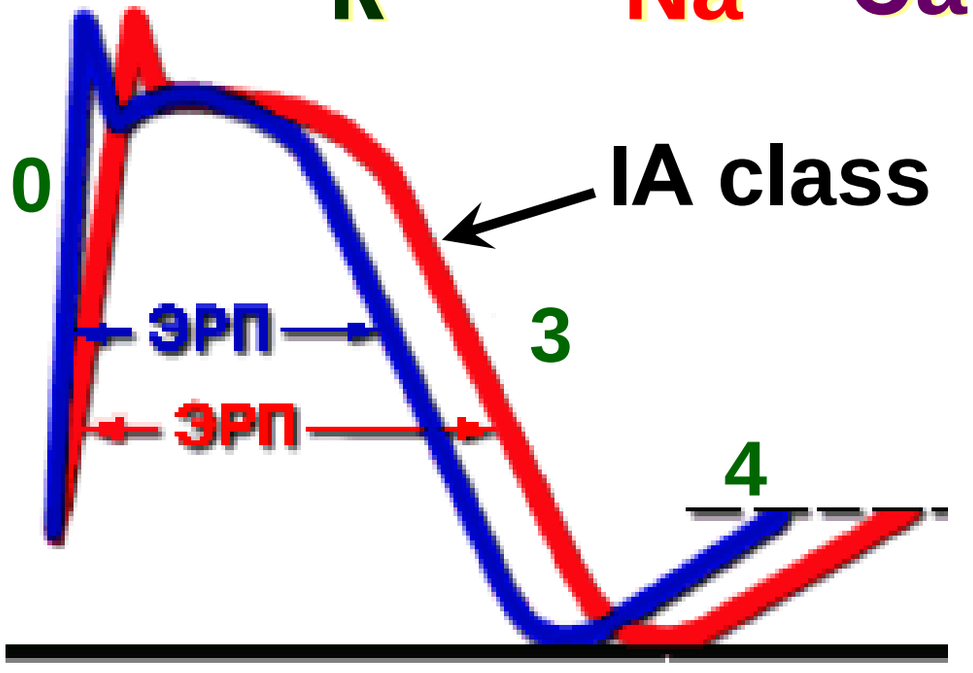
| *Subgroup* | ↓ speed of rapid depolarization | duration of action potential |
|---|---|---|
| I A | ++ | ↑ |
| I B | + | ↓ |
| I C | +++ | - |

# IA SUBGROUP (quinidine-like)

- ✓ block $Na^+$-channals and slow-down depolarization (phase 0 – excitability and 4 – automaticity)



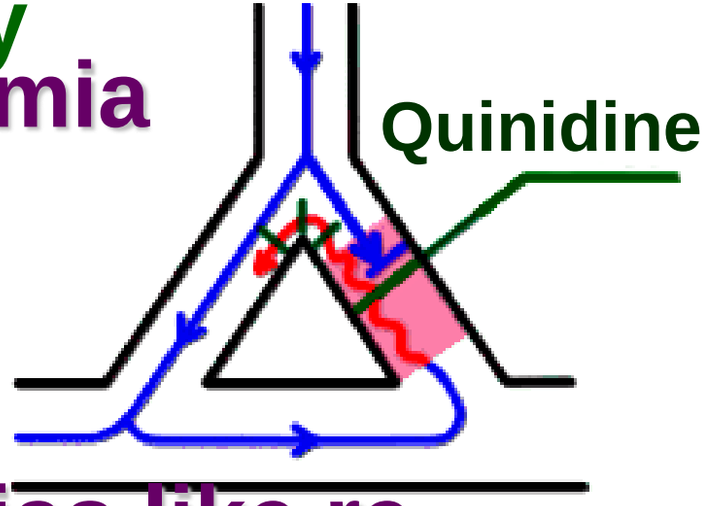




- ✓ block $K^+$ -channels and slow-down repolarisation (phase 3)
- ✓ ⇒ ↑ AP and ↑ ERP

- ➢ ↓ automaticity, excitability, and conductivity
- ➢ vagolytic action on SA and AV-nodes

# IA SUBGROUP (quinidine-like)

- on SA-node: ↓ automaticity, ↑ vagolytic effect ⇒ insignificant tachycardia
- on AV-node: ↓ automaticity and conductivity, ↑ vagolytic effect ⇒ in case of supraventricular tachyarrhythmia
- on Purkinje fibers:
  - ↓ automaticity and excitability ⇒ in ventricular tachyarrhythmia
  - ↑ ERP ⇒ in tachyarrhythmia resulted from impulses circulated in closed chains




  - ↓ conductivity ⇒ in arrhythmias like re-entry (transformation one-way block into complete block)

# IA SUBGROUP

## Quinidine

- «-» inotropic action
- peripheral vasodilation (α-adrenolytic action)
- ↓ BP (↓ cardiac output and peripheral vascular resistance)

### indications:

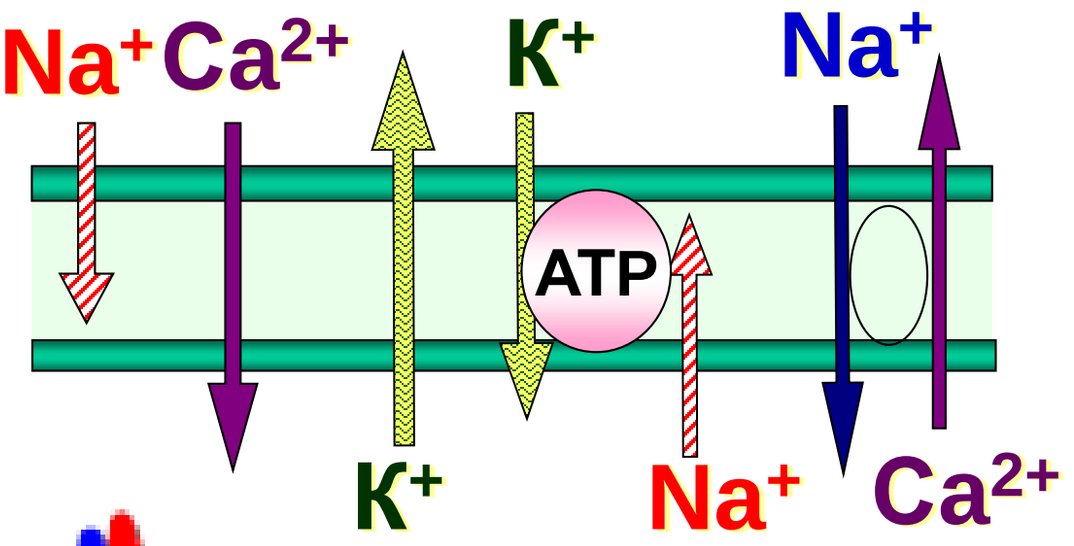
- atrial fibrillation
- supra-ventricular and ventricular paroxysmal tachycardia
- supra-ventricular and ventricular extrasystoles

### adverse effects:

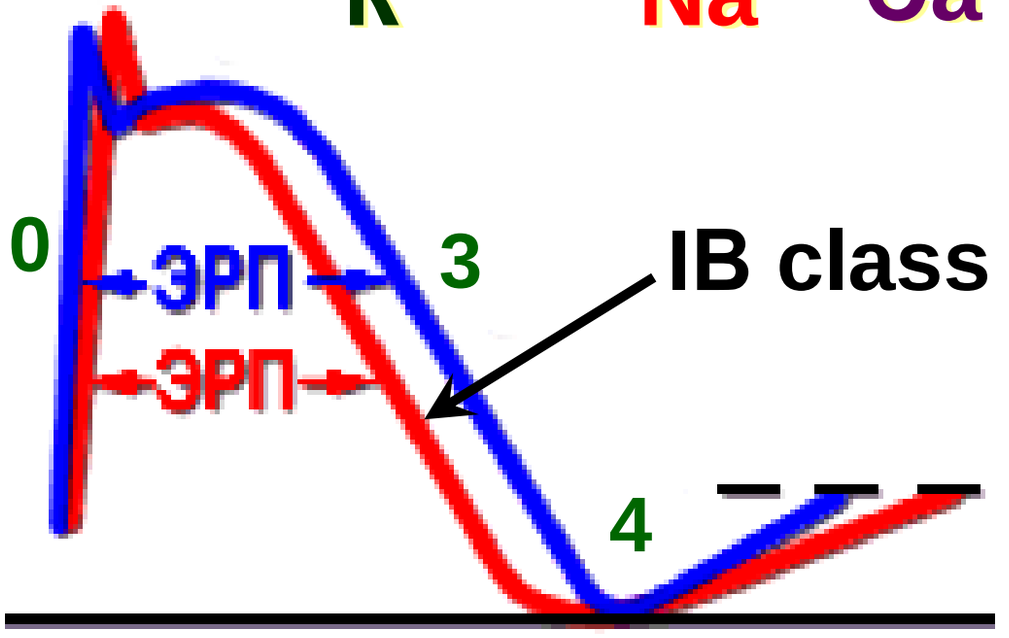
- ↓ contractility, ↓ BP, AV-block
- hearing and visual disturbances, dyspepsia, allergic reactions etc.

# IB SUBGROUP (lidocaine)

- ✓ blocks $Na^+$-channels and slows down the depolarization (phase 0 – excitability and 4 – automaticity)




- ✓ ↑ permeabiity of $K^+$ and ⇒ speeds up the repolarization (phase 3)
- ✓ ⇒ ↓ AP and ↓ ЭРП (ERP)




- ➢ ↓ automaticity, excitability and conductivity (<, than IA subgroup)
- ➢ causes weak suppressive action on AV-node

# IB SUBGROUP

## indications:

- ventricular extra-systoles, for example in myocardial infarction (lidocaine – 2 % sol. I.V. by drops, 10 % sol. I.M.; mexilethin – I.V., oral), cardioversion
- arrhythmia cause by cardiac glycosides (diphenin, lidocaine)

## adverse effects:

- arrhythmia (AV-block etc.)
- neurological (paresthesia, tremor, impairment of hearing, convulsions)

# II class – BETA-ADRENOBLOCKERS

- ***non-selective ($\beta_1$+ $\beta_2$):*** **propranolol (anaprilin), nadolol, timolol**
- ***selective ($\beta_1$):*** **metoprolol, atenolol, bisoprolol, acebutolol, celiprolol**
- ***with intrinsic sympathomimetic activity:*** **oxprenolol, pindolol**

## cardiac effects

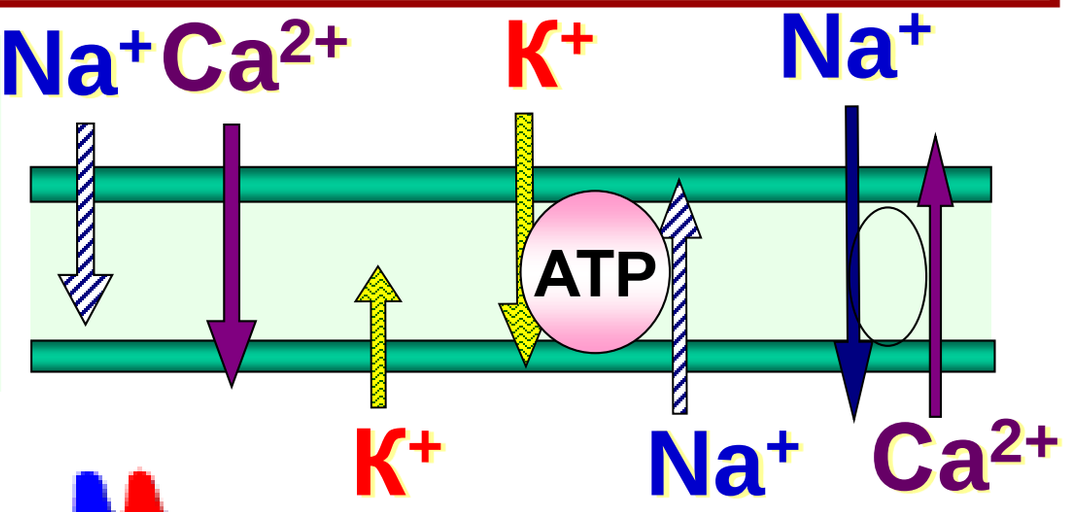
- ↓ automaticity of SA-node
- ↓ automaticity and conductivity of AV-node
- ↓ automaticity of Purkinje fibers
- «-» ino- and chronotropic effects
- ↓ oxygen consumption of myocardium

## indications

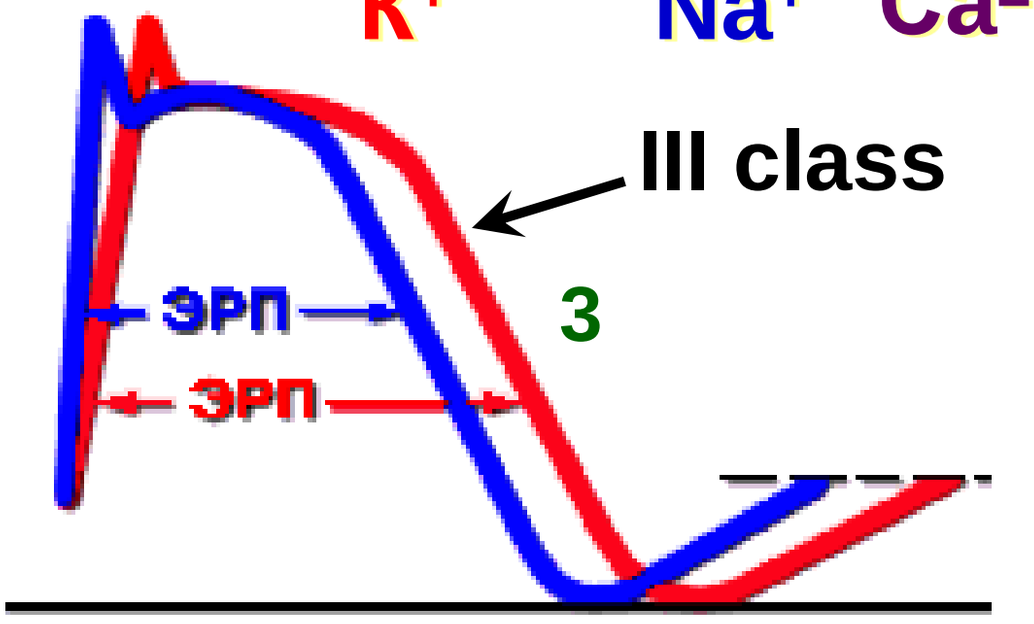
- supra-ventricular tachyarrhythmia and extrasystoles
- ventricular extrasystoles caused by raising of automaticity

# III class – POTASSIUM CHANNEL BLOCKERS (amiodarone)

- ✓ blocks $K^+$-channels and ↓ repolarization (phase 3)
- ✓ ⇒ ↑ AP and ↑ ЭРП (ERP)




- ✓ blocks $Na^+$- and $Ca^{2+}$-channels
- ✓ β-adrenolytic effect




- ➢ shares activity IA, II, and IV classes as well

- ➢ «-» ino-, chronotropic effects
- ➢ ↓ AV-conductivity

# III class – POTASSIUM CHANNEL BLOCKERS (amiodarone)

## indications

- different types of tachyarrhythmias and extrasystoles, including those that are drug-resistant
- angina pectoris, stenocardia

## adverse effects

- arrhythmia (AV-block, bradycardia etc.), hypotension
- at long-lasting therapy (cumulate, T1/2 upto 100 days!):
  - ✓ tremor, ataxia, paresthesia
  - ✓ hypo- or hyperthyroidism
  - ✓ pulmonary fibrosis
  - ✓ liver dysfunction, constipation
  - ✓ yellow-brownish precipitates in cornea, visual impairment
  - ✓ photodermatitis (grey-blue skin discolouration), photosensibilization etc.

# IV class – CALCIUM CHANNEL BLOCKERS (CCB)

## General characteristics

**Calcium channels blockers (CCB)** — are the agents that decrease the influx of calcium ions predominantly via L-type potential-dependent («slow») calcium channels

## History of inventions

**1961 y.** Dr. F. Dengel synthesized **verapamil** when he was trying to create synthetic analogues of papaverin

**1967 y.** A. Flekenstein unveiled the mechanism of its action and proposed the name «calcium antagonists»

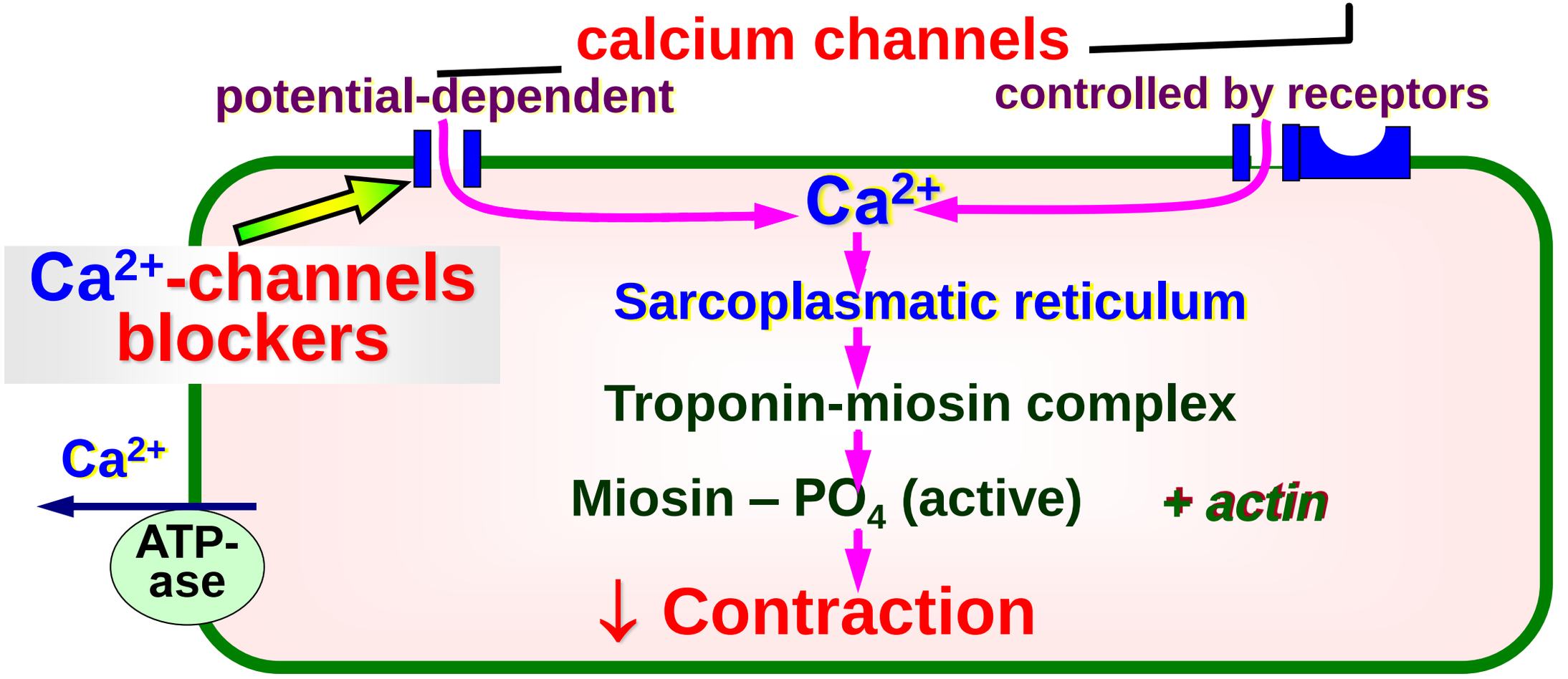
**1966 and 1971 yy.** **nifedipine** and **dilthiazem** (correspondently) were got

# CLASSIFICTION OF CALCIUM CHANNEL BLOCKERS

- **I type – cardio-tropic *(phenylalkylamine derivatives):* *1 generation* – verapamil, *2 generation* – hallopamil etc.**
- **II type (vaso-tropic):**
  - ✓ **systemic action: *dihydro-pyridine derivatives (DCCB): 1 generation* – nifedipine, *2 generation* – nifedipin-GITS, amlodipine, isradipine, nicardipine, nimodipine* etc.**
  - ✓ **cerebro-vaso-tropic –*diphenyl-piperasine derivatives: 1 generation* – cinnarisine, *2 generation* – flunarisine as well as certain dihydro-pyridine derivatives* (nimodipine)**
- **III type – mixed *(benzothiazine derivatives): 1 generation* – dilthiazem, *2 generation* – clenthiazem**

# MECHANISM OF ACTION OF CCB

↓ intracellular influx of $Ca^{2+}$ through L–type potential-dependent calcium («slow») channels (myocardium, smooth muscles of blood vessels, bronchi, GIT, myometrium, and thrombocytes) by binding with them and changing their modality (↑ and/or ↓ duration of different phases), but not by blockage of that channels or antagonism to $Ca^{2+}$ (!)



# PHARMACODYNAMICS OF CCB

## differ by:

- ✓ chemical structure
- ✓ sites of binding at calcium channels
- ✓ tissue specificity

*The selectivity of DCCB nifedipine and amlodipine concerning blood vessels 10 times, felodipine — 100 times, nisoldipine — 1000 times more comparatively to verapamil and dilthiazem, nimodipine has selectivity for cerebral vessels, nisoldipine — for coronary vessels, felodipine — both for coronary and peripheral arteries*

## ⇒ Difference in influencing on cardio-vascular system:

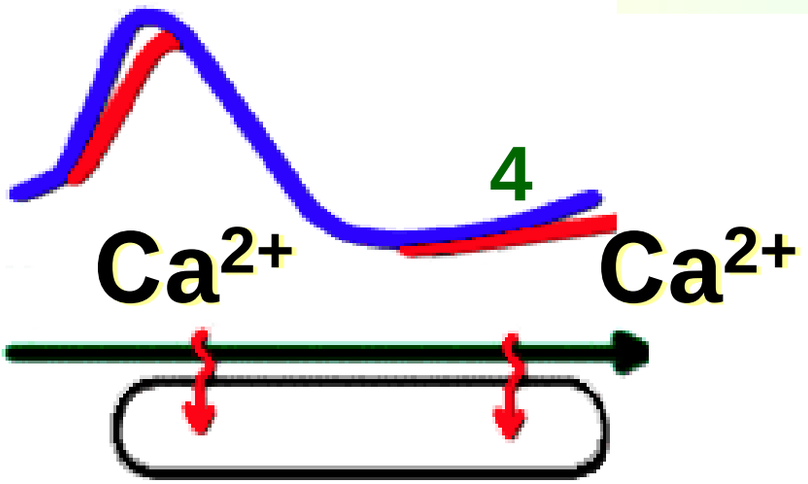
- **vasotropic (DCCB):** prominant vasodilation, weak influence on contractility and absence of action on conductivity ⇒ **hypo-tensive and anti-anginal actions**
- **cardio-tropic (verapamil) and mixed (dilthiazem):** вsignificant impact on contractility, conductivity, and automaticity of myocardium, moderate vasodilation ⇒ **anti-anginal, anti-arrhythmic, and hyp-tensive actions**

# PHARMACODYNAMICS OF CCB

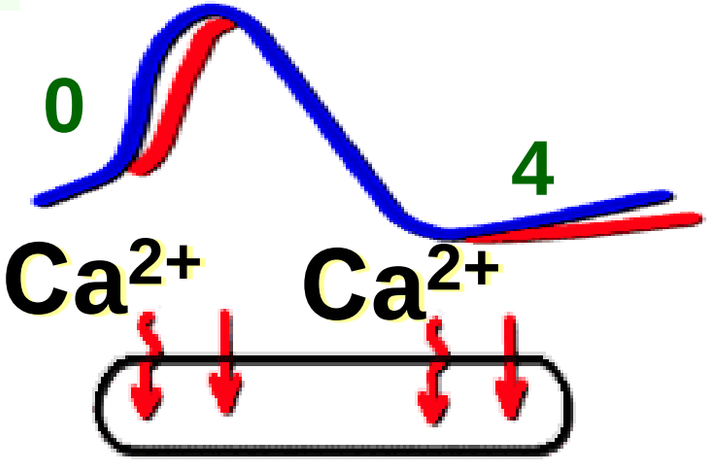
- **blood vessels (basicely in DCCB) – vasodilation (predominantly of vessels) ⇒**
  - ↓ peripheral resistance ⇒ ↓ ABP ⇒ hypotensive action
  - ↓ peripheral resistance results in ↓ cardiac after-load ⇒ ↓ $O_2$ consumption of myocardium + ↓ coronary spasm ⇒ ↑ coronary blood flow into ischemic zones ⇒ ↑ $O_2$ supply of myocardium ⇒ anti-anginal action
  - ↓ cerebral vasoconstriction and consequences of brain stroke (nimodipine, cinnariциннаризин) ⇒ cerebro-protection
- **heart (verapamil, dilthiazem):**
  - «-» ino- and chronotropic effects, ↓ cardiac output ⇒ ↓ $O_2$ consumption of myocardium ⇒ anti-anginal action
  - ↓ SA-node automaticity, ↓ ectopic areas in atrium, ↓ AV-conductivity ⇒ «-» bathmo- and dromo-tropic effects ⇒ anti-arrhythmic action
  - cardio-protective action ⇒ regress of left ventricular hypertrophy

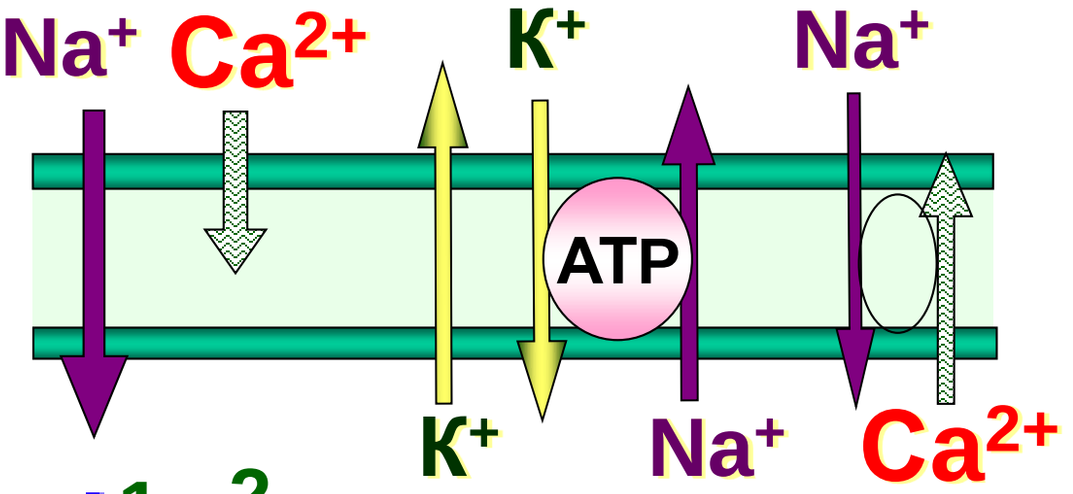
# IV class – CALCIUM CHANNELS BLOCKERS (verapamil, dilthiazem)

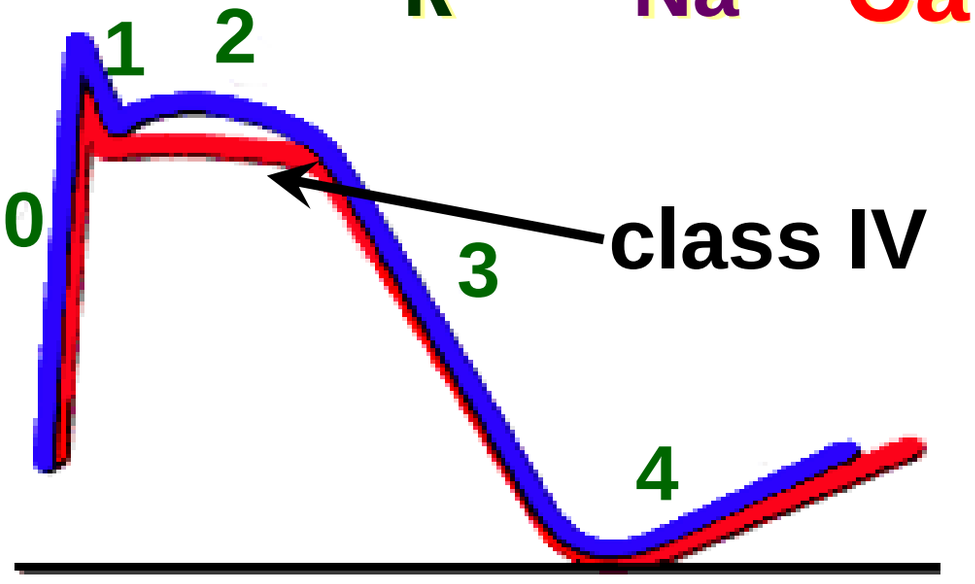
↓ automaticity of SA-node (phase 4)




↓ conductivity (phase 0) and automaticity (phase 4) of AV-node



# PHARMACODYNAMICS OF CCB

- **kidneys:**
  - ↓ vasoconstriction of renal vessels, ↑ renal blood flow ⇒ **nephroprotective** effect
  - ↑ rate of glomerular filtration + ↓ sodium reabsorption ⇒ **diuretic** effect (contribute into hypotensive effect)
- **smooth muscles of internal organs:**

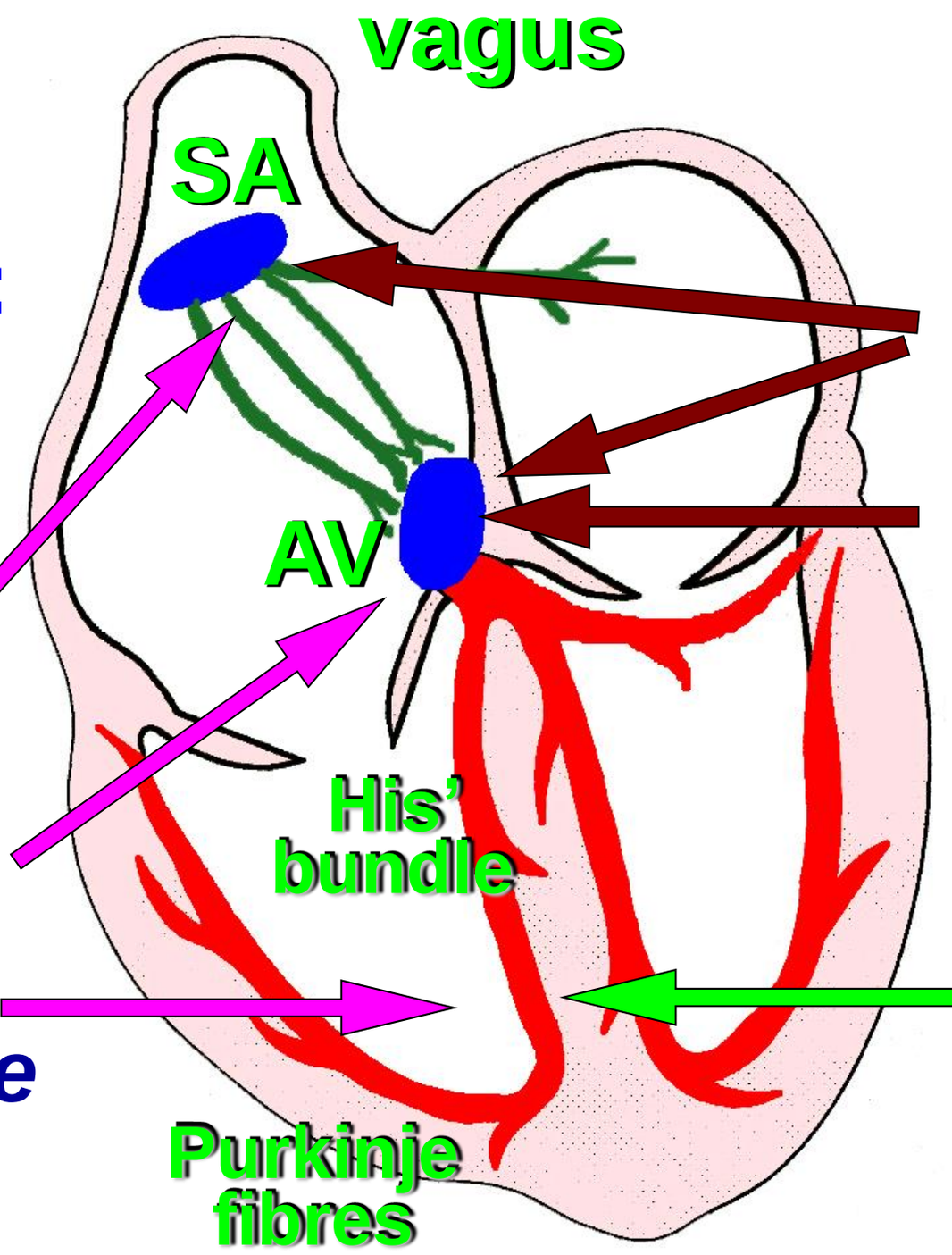
  relaxation ⇒
  - ↓ bronchospasm ⇒ **broncholytic** effect
  - ↓ GIT tonus ⇒ **spasmolytic** effect
  - ↓ uterus tonus ⇒ **tocolytic** effect
- **blood:** ↓ platelets aggregation and thromboxane $A_2$ и ⇒ **anti-aggregative** action
- **metabolism:**
  - ↓ development of atherosclerosis ⇒ **anti-atherosclerosis** action
  - ↓ lipids peroxydation, that prevent formation of free radicals

# INDICATIONS FOR CCB

- supra-ventricular extra-systoles and tachyarrhythmia, atrial flutter and fibrillation (verapamil, dilthiazem)
- angina pectoris: efforts angina, vasospastic angina) (verapamil, dilthiazem, DCCB of II generation)
- arterial hypertension
- disturbance of cerebral blood flow, migraine (nimodipine, cinnarizin)
- impairment of peripheral blood flow, Reyno disease (amlodipine)
- in complex therapy of CNS disorders: Alzheimer disease, dementia, alcoholism, vestibulopathy (nimodipine)
- for prevention of cold air-caused bronchospasm

# SITES OF ACTION OF ANTI-ARRHYTHMICS

**At supra-ventricular and ventricular:**




*quinidine-like*

*beta-adreno-blockers*

*amiodarone*

**At supra-ventricular only:**

*verapamil*

*cardiac glycosides*

**At ventricular only:**

*lidocaine*

*diphenin*